Brand versus generic medications: the money, the patient and the research

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Despite having a prescription for a specific brand medication, we are often served a generic drug and, often but not always, told that it is "the same" but less expensive. Is it really? Some generics of old medications such as the benzodiazepines and the tricyclics are really inexpensive, with most of the bill going toward pharmacy costs. As an example, the price of a low dose of amitriptyline for the management of chronic pain for 1 month is probably not much more than that of a cappuccino in a fancy bistro. In contrast, the savings on newer molecules introduced immediately after patent expiration are not that considerable. This is, in part, due to the fact that generic companies, like brand companies, are in the business to make money. In addition, the chemical synthesis of some medications may be quite cumbersome and expensive. For instance, generic companies stayed away from making the commonly used antibiotic cefaclor because its synthesis involves an intermediate that is explosive.

After a patent for an original medication has expired, companies producing generics initially have to present data showing that their product has 80%–125% bioavailability of the original drug. Variations within that range for most illnesses and most patients probably have no clinical consequences. In some cases, however, a switch to a generic will produce a significant difference in the control of a disorder, for instance, in the management of epilepsy when the outcome is not a mere alteration of a biochemical parameter. The change can be quite obvious indeed. In the management of high blood pressure, whereby the primary target parameter can easily be monitored by the patient at no cost, the loss of adequate control can be easily documented. In the United States, some health management organizations will pay for some brand medications, despite the availability of generics, because the savings that can be achieved by switches to generics are often offset by subsequent patient visits to practitioners for stabilization of the blood pressure. Several years ago in Canada, clinicians witnessed relapses in some patients previously doing well on Prozac after a switch to generic fluoxetine.[1] The same phenomenon is now occurring in the United States with the expiration in the Prozac patent in 2002.

What could account for such changes in treatment response? As mentioned, the production of medications is a complex procedure involving numerous steps, each one having its own yield that can vary with minimal alterations in the synthesis conditions. At the end of the synthetic chain for a given batch, the final product should reach the minimal 80% cut-off when given orally. How rigorous is the observance of this criterion by the companies producing generics after the initial demonstration? It is fair to state that the burden of proof is on them, given the occasional destabilization of a patient's condition when the only additional variable is the switch to a generic drug. In such cases, the re-introduction of the original drug and the restoration of the therapeutic effect constitutes a very convincing hypothesis validation.

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Another factor that may be associated with an ineffective switch from an original to generic drug is the possibility that impurities can be left behind at some of the synthesis steps. Regulations concerning the presence of such by-products are much more difficult to formalize, in contrast to those regulating bioavailability equivalence. In addition, the concentration of impurities need not be elevated to be problematic. A good example of this is the tryptophan catastrophe that occurred in the United States in the early 1990s. Tryptophan production is quite complex and fairly expensive. An overseas firm manufacturing health foodstuffs modified their procedure to produce tryptophan. As a result of a contaminant being left behind, 36 individuals died and numerous others were left with permanent neurological sequelae due to the eosinophilia-myalgia syndrome.[2] These figures likely represent an underestimate of the magnitude of the problem.[3] Until then, tryptophan was only available by prescription from a single brand company in Canada. The only tryptophan intoxication cases recorded in Canada were individuals who had purchased tryptophan supplements from the United States. As a result, tryptophan was never removed from the market in Canada. The subsequent introduction of a generic for tryptophan aborted a double-blind study in our research unit on the effectiveness of a Visken-Tryptan (pindolol-tryptophan) augmentation in patients with obsessive–compulsive disorder who were not responding to a serotonin reuptake inhibitor. Indeed, the producer of the original tryptophan, with an already limited market, decided not to fund the study, as would be expected from a business point of view. Limited patent life may obviously restrict research investments.

The cessation of research funding by large pharmaceutical firms after the expiration of their patent for a brand medication is a major setback for research at large. Indeed, quality of life and life expectancy have markedly increased in the last century, in part, due to advances in pharmacology fueled by drug development by pharmaceutical firms. Enormous amounts of money are invested in drug development, but an infinitesimal number of all the compounds synthesized and tested eventually make it to the market. Although scrutiny has to be exerted to prevent brand companies from over-pricing new drugs, there should also be rigorous surveillance of cost setting for generic drugs, considering that generic companies have absolutely no financial recovery to make from research investments — because they do not have any. On the public side, one has to question priorities when complaining of $75 prescriptions to treat a bronchitis or a depression, while readily accepting such an hourly fee at car dealerships, parts not included. Ironically, more people die from suicide every year in Quebec than from car accidents.

To conclude, I would like to present the following patient vignette to illustrate some of the above-mentioned points. In a physical examination before cataract surgery, a 74-year old male patient was found to have hypertension. His blood pressure was 220/120 mm Hg without tachycardia. After a work-up, the internist prescribed amlodipine, 5 mg daily. After 2 weeks and an increase in dosage to 10 mg/d, the patient's blood pressure remained unaltered. A physician from the patient's family switched him to Visken (pindolol), 5 mg twice a day. Two days later, his blood pressure was at 150/90 mm Hg with a heart rate in the low 70s. Upon regular follow-ups over the next 2 years, his blood pressure never went above the later figures. Then, the patient had a fainting spell in his apartment, after which his blood pressure was found to be 220/120 mm Hg. Medication compliance did not appear to be an issue, but the same "family" physician realized that the patient had been switched to a generic ($30.25/mo v. $36.56/mo for the brand medication). The original brand was immediately restored, and 2 days later blood pressure was back down to 150/90 mm Hg. My father subsequently died from a dissected aorta, a well-known complication of high blood pressure.

Competing interests: Dr. Blier has served as a consultant for Organon Pharmaceuticals, Eli Lilly and Company, Asahi Pharmaceuticals, Merck, Forest Laboratories, Janssen Pharmaceuticals and Bristol-Myers Squibb; on the speaker's bureau of Organon Pharmaceuticals, Eli Lilly and Company, Pfizer, Forest Laboratories, Janssen Pharmaceuticals and GlaxoSmithKline; has received grant funding from Organon Pharmaceuticals, Eli Lilly and Company and Merck; and has been a contract employee of Forest Laboratories, Janssen Pharmaceuticals and Steel Beach Productions.

References

1. Bakish D, Miller C, Hooper C, Cavazzoni P, Thibaudeau C, Atwood D, Layton S. A double-blind, crossover study comparing generic and brand fluoxetine in the treatment of major depression [abstract]. NCDEU 40th Annual Meeting. 2000 May 30 – June 2. Boca Raton (FL). Abstract no. 206.
2. Swygert LA, Back EE, Auerbach SB, Sewell LE, Falk H. Eosinophilia-myalgia syndrome: mortality data from the US national surveillance system. *J Rheumatol* 1993;20:1711-7.
3. Sullivan EA, Kamb ML, Jones JL, Meyer P, Philen RM, Falk H, et al. The natural history of eosinophilia-myalgia syndrome in a tryptophan-exposed cohort in South Carolina. *Arch Intern Med* 1996;156:973-9.